IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: **Chapman and King** Confirmation No.: **3379**

Serial No.: **09/719,045** Art Unit: **1644**

Filed: **December 7, 2000** Examiner: **David A. Saunders**

Title: DIVALENT ANTIBODY FRAGMENTS Customer No.: **34133**

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DATE OF DEPOSIT: January 26, 2007

MAIL STOP APPEAL BRIEF- PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

APPEAL BRIEF UNDER 37 CFR § 41.37

This is an appeal from the Final Rejection dated as mailed March 29, 2006, rejecting claims 1-10 and 12-15 in the above-identified application. A Notice of Appeal and Request for Pre-Appeal Brief Conference were filed June 22, 2006. A Notice of Panel Decision from Pre-Appeal Brief review, dated as mailed July 26, 2006, advised that the application remained under appeal. A petition for a five-month extension of time and the appropriate fee accompany this brief. The brief fee also accompanies this brief.

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REAL PARTY IN INTEREST

The real party in interest is UCB S.A. A document evidencing the same will be recorded in due course. The previous real party in interest was Celltech R & D, Ltd. (formerly Celltech Therapeutics, Limited).

RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences which will directly affect, will be directly affected by, or have a bearing on the Board's decision in the present appeal.

STATUS OF CLAIMS

The claims pending in this application are Claims 1-15. Claims 1-10 and 12-15 stand rejected. Claim 11 was objected to as depending upon a rejected base claim. The pending claims are appended hereto in the Claims Appendix.

STATUS OF AMENDMENTS

All amendments have been entered.

SUMMARY OF CLAIMED SUBJECT MATTER

The claims of the present application are directed to divalent antibody fragments comprising two antibody heavy chains (page 3, lines 25-27) and at least one polymer molecule that increases the circulating half-life of the fragments (page 2, lines 1-14, and Table 2) attached to the heavy chains in a site-specific manner on each chain (page 3, lines 14-17) outside of the variable region domain of each chain (page 3, line 31). By attaching the polymer molecules in a site-specific manner, the loss of immunoreactivity when using a random attachment process is avoided (page 3, lines 17-20).

Claim 1 is the only independent claim. Support for the recitations in claim 1 is shown in the table below.

1. A divalent antibody fragment comprising two antibody heavy chains and at least one polymer molecule effective for increasing the circulating half-life of said fragment in covalent linkage,	page 3, lines 25-27 and page 2, lines 1-14
each heavy chain being covalently linked to the other by at least one non-disulphide interchain bridge linking the sulphur atom of a cysteine residue in one chain to the sulphur atom of a cysteine residue in the other chain,	page 3, lines 27-30
said cysteine residues being located outside of the variable region domain of each chain,	page 3, lines 30-31
characterised in that the at least one non-disulphide interchain bridge contains the at least one covalently linked polymer molecule.	page 3, lines 31-33

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

There are two grounds of rejection presented for review. The first ground of rejection is the rejection of claims 1-10, 12-13, and 15 under 35 U.S.C. § 102(e) as allegedly anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as allegedly obvious over, Gonzales et al (U.S.

Patent No. 6,025,158). The second ground of rejection is the rejection of claims 1 and 13-14 under 35 U.S.C. § 103(a) as allegedly obvious over, Gonzales et al in view of Barbanti et al (U.S. Patent No. 5,436,154).

ARGUMENT

Claims 1-10, 12-13, and 15 are not anticipated by, nor obvious over, Gonzales et al

Claims 1-10, 12-13, and 15 were rejected under 35 U.S.C. § 102(e) as allegedly anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as allegedly obvious over, Gonzales et al. Gonzalez et al, however, does not disclose or suggest the invention of Appellants' claim 1. Claims 2-10, 12-13, and 15 depend from claim 1. Thus, Gonzalez et al does not disclose or suggest the invention of these claims either. More specifically, Gonzalez et al does not disclose or suggest a divalent antibody fragment having a polymer molecule covalently linked to a cysteine residue outside of the variable region domain **on each heavy chain**.

The Office continues to combine isolated sections from Gonzalez et al in contradistinction of Gonzalez et al's disclosure, and in contradistinction of the case law. For a reference to anticipate, each limitation of the claim, **arranged as in the claim**, must be present in a single reference. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir 1989), emphasis added. This requirement is not met by Gonzalez et al., either expressly or inherently. Gonzalez et al describes **monovalent** antibody fragments conjugated to a high molecular weight polymer by a hinge region cysteine, and describes two antibody fragments linked together by polymer molecules (col. 35, lines 45-48), without specifying how and where, they are attached. What Gonzalez does not describe is two antibody

fragments linked together by a polymer molecule through a cysteine residue outside the variable region domain on **each** fragment, either expressly or inherently. In apparent recognition of this, the Office has argued that such "is clearly within the 4 corners or the reference." (See Final Rejection, page 3.) But, the standard for anticipation is not that something be within the 4 corners of a reference, rather, it is that the reference disclose each limitation of the claim, arranged as in the claim.

Neither is the claimed antibody fragment inherent from Gonzalez et al. To establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference...Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing **may** result from a given set of circumstances is not sufficient." MPEP 2112, IV, citing *In re Robertson*, 169 F.3d 743, 745, 49 U.S.P.Q.2d 1949, 1950-51 (Fed. Cir. 1999), emphasis added.

As Appellants argued previously, the claimed divalent antibody fragments are not necessarily present in Gonzalez et al. In fact, whenever Gonzalez et al specifically discusses attaching polymer molecules to a cysteine residue on one chain of a divalent antibody fragment, i.e., $F(ab')_2$, it requires that the corresponding cysteine residue in the opposite chain be substituted with another amino acid. See, for example, col. 21, lines 50-59; col. 23, lines 17, through col. 24, line 27; and col. 31, line 55, through col. 33, line 2. The Office attempted to dismiss these references as simply Appellant's focusing upon one genre of embodiments. What the Office continues to ignore, however, is that the disclosure of this genre contradicts any arguments of inherency by clearly establishing that divalent antibody fragments attached to a

polymer through a cysteine residue outside the variable region on each chain are not **necessarily present** in Gonzalez et al.

Indeed, as Appellants have argued previously, the foregoing passages actually teach away from Appellants' claimed invention, thereby defeating any argument of obviousness over Gonzalez et al. A prior art reference must be considered in its entirety, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). When Gonzalez et al is considered as a whole, particularly the passages concerning substituting the cysteine on the second chain, it leads away from Applicants' invention.

As further evidence of teaching away, Gonzalez et al describes making the divalent antibody fragments using polymer molecules derivatized with "**multiple functional groups**" to permit the attachment of two or more antibody fragments to the polymer backbone. See column 35, lines 45-57. The use of multiple functional groups suggests multiple attachment locations on each chain of the antibody fragment, not the same location on each heavy chain, much less a cysteine residue on each heavy chain. Indeed, Gonzales et al lists a variety of crosslinking sites on the antibody fragments that can be used, e.g., N-terminal amino groups and epsilon amino groups found on lysine residues, amino groups, imino groups, carboxyl groups, sulfhydryl groups, hydroxyl groups, and other hydrophilic groups (See column 41, lines 63-57).

As is clear from the foregoing, the Office has failed to establish a *prima facie* case of obviousness.

To establish a *prima facie* case of obviousness, three basic criteria must be met.

First, there must be some suggestion or motivation, either in the references

> themselves or in the knowledge generally available to one of ordinary skill in the art, to **modify the reference** or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure.

MPEP 706.02(j), citing *In re Vaeck,* 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991), emphasis added.

Surprisingly, in the Final Rejection, the Office accuses Appellants of obfuscating the issues by pointing out these teachings away in Gonzalez et al, alleging that they ignore the "clear teaching the Fab' fragments were engineered [to have a] free cysteine in the hinge region that was used to attach the PEG molecule." *See* page 3 of the Final Rejection. First, Fab' fragments are monovalent, not divalent. Second, Appellants are not obfuscating the issues by relying upon all the teachings of the reference but, rather, following legal precedent. *See W.L. Gore, supra.*

Indeed, the Office would not have been able to reconstruct Appellants' invention from Gonzalez et al without the inappropriate use of hindsight. *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."). It is of no consequence that the isolated disclosures come from a single reference in this instance. The standards for establishing obviousness must still be met. It is incumbent upon the Office to provide a reason why one of ordinary skill in the art would have been led to modify a prior art

reference or to combine reference teachings to arrive at the claimed invention. *Ex parte Clapp*, 227 U.S.P.Q.2d 972 (Bd. Pat. App. Int. 1985). The requisite motivation must stem from some teaching, suggestion or inference in the prior art as a whole or from the knowledge generally available to one of ordinary skill in the art and not from Appellants' disclosure. *See*, for example, *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 5 U.S.P.Q.2d 1434 (Fed. Cir. 1988). The Office has not provided motivation to modify the teachings of Gonzalez et al to arrive at the claimed invention

Appellants respectfully submit that this rejection is inappropriate and should be withdrawn.

Claims 1 and 13-14 are not obvious over Gonzales et al in view of Barbanti et al

Claims 1 and 13-14 were rejected under 35 U.S.C. § 103(a) as allegedly obvious over Gonzalez et al in view of Barbanti et al. The deficiencies of Gonzalez et al are discussed above, discussion incorporated herein. Barbanti et al does not overcome these deficiencies. Barbanti et al is relied upon by the Office for the description of anti-TNF antibody fragments. Barbanti et al does not provide the motivation to modify Gonzalez et al to result in the invention of claim 1. Claims 13-14 depend from claim 1 and, thus, are not rendered obvious over Gonzalez et al in view of Barbanti et al.

The Office relies upon column 16, lines 39-46, of Gonzalez et al for allegedly teaching that the benefits of extended circulating half-life gained by conjugation to a polymer were to be expected without regard to antigen specificity. The Office then misquotes Gonzalez et al in alleging that it provided motivation to modify antibody fragments to be pegylated. The Office states that "Gozales [sic] et al teach that 'PEGlaytion' [sic] of antibody fragments has been

shown to extend serum half-life to useful levels." Column 1, lines 29-32 of Gonzalez et al is cited. (See Final Rejection, page 4.) The actual quote reads ". . .PEGylation has **not** been shown to extend serum half-life to useful levels." (See column 1, lines 31-32, of Gonzalez et al, emphasis added.) The Office, based upon its misquote, interprets these passages to teach not only that antibody fragments, regardless of their antigen specificity, do not have sufficient serum half-life to be useful (which Appellants contend is an inappropriate reading into the reference), but also to provide motivation to couple any antibody fragment to a polymer such as PEG. Clearly, they do not.

The Office also takes the position that the motivation to apply the teachings of Gonzalez et al to Barbanti et al is implicit from Barbanti et al itself. The Office notes that Barbanti et al teach that the anti-TNF antibodies can be used to treat numerous conditions, including those that are chronic. The Office then contends that one would have been motivated to extend the half-life of anti-TNF antibody fragments, "at the very least, for those situations in which there is chronic hyperproduction of TNF, in order to obtain a more extended therapeutic effect for any single treatment." (See Office Action, page 4.) There are two glaring flaws to the Office's reasoning. First, Barbanti et al gives absolutely no suggestion that serum half-life is considered to be a problem, or that longer serum half-lives are desired. Second, the Office is focusing upon a single treatment. Barbanti et al, however, clearly contemplates multiple administrations over time (see column 22, lines 39-44).

Appellants respectfully submit that this rejection is inappropriate and request that it be withdrawn.

CONCLUSION

Claims 1-10 and 12-15 are not anticipated by, or obvious over, the art cited by the Office.

Appellants request that all rejections be withdrawn and that all claims be allowed.

Respectfully submitted,

Date: January 26, 2007

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CLAIMS APPENDIX

Claim 1 A divalent antibody fragment comprising two antibody heavy chains and at least one polymer molecule effective for increasing the circulating half-life of said fragment in covalent linkage, each heavy chain being covalently linked to the other by at least one non-disulphide interchain bridge linking the sulphur atom of a cysteine residue in one chain to the sulphur atom of a cysteine residue in the other chain, said cysteine residues being located outside of the variable region domain of each chain, characterised in that the at least one non-disulphide interchain bridge contains the at least one covalently linked polymer molecule.

Claim 2 An antibody fragment according to Claim 1 in which each heavy chain is covalently linked to the other by a single non-disulphide bridge, said bridge containing a covalently linked polymer molecule effective for increasing the circulating half-life of said fragment.

Claim 3 An antibody fragment according to Claim 1 wherein each heavy chain is paired with a light chain.

Claim 4 An antibody fragment according to Claim 1 wherein each heavy chain is a V_H-CH1 chain terminally substituted by a hinge region domain.

Claim 5 An antibody fragment according to Claim 4 wherein each non-disulphide bridge present links the sulphur atom of a cysteine residue located in the hinge region domain of one heavy chain, to the sulphur atom of a cysteine residue in the hinge region domain of the other chain.

Claim 6 An antibody fragment according to Claim 1 wherein the polymer is an optionally substituted straight or branched chain polymer selected from the group consisting of polyalkylene, polyalkenylene and polyoxyalkylene, or a branched or unbranched polysaccharide.

Claim 7 An antibody fragment according to Claim 6 wherein the polymer is an optionally substituted straight or branched chain polymer selected from the group consisting of poly(ethylene glycol) or a derivative of poly(ethylene glycol).

Claim 8 An antibody fragment according to Claim 7 wherein the polymer is selected from the group consisting of methoxy(polyethylene glycol) or a derivative of methoxy(polyethylene glycol).

Claim 9 An antibody fragment according to Claim 8 wherein the polymer has a molecular weight in the range from about 25000Da to about 40000Da.

Claim 10 An antibody fragment according to Claim 1 wherein each interchain bridge is the residue of a homo- or heterobifunctional cross-linking reagent.

Claim 11 An antibody fragment according to Claim 10 wherein each bridge is an optionally substituted C_{4-20} alkylene chain optionally interrupted by one or more heteroatoms or heteroatom-containing groups.

Claim 12 An antibody fragment according to Claim 1 which is covalently attached to one or more effector or reporter molecules.

Claim 13 An antibody fragment according to Claim 1 which is able to selectively bind to a cell surface or soluble antigen.

Claim 14 An antibody fragment according to Claim 13 wherein the antigen is human tumour necrosis factor-α or a platelet derived growth factor or a receptor thereof.

Claim 15 A pharmaceutical composition comprising an antibody fragment according to any of the preceding claims together with one or more pharmaceutically acceptable excipients, diluents or carriers.

EVIDENCE APPENDIX

NONE

RELATED PROCEEDINGS APPENDIX

NONE